

WE CLAIM:

1. A method for inhibiting proliferation and inducing cell death in a population of cancer cells by (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity within the population.
2. The method of claim 1 wherein the amount of *MDA-7* is increased by introducing, into one or more cell of the population, a nucleic acid encoding *MDA-7* protein in expressible form.
3. The method of claim 2 wherein the nucleic acid encoding *MDA-7* protein is comprised in a viral vector.
4. The method of claim 3 wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.
5. The method of claim 1 wherein *RAS* activity is decreased by administering, to the cancer cell population, an effective amount of an anti-*RAS* agent, which may be, for example, an antisense molecule, a ribozyme, a precursor of a triple helix, or a farnesyl transferase inhibitor.
6. The method of claim 5, wherein *RAS* activity is decreased by administering an effective amount of a viral vector encoding an antisense molecule.
7. The method of claim 6, wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.
8. The method of claim 5, wherein *RAS* activity is decreased by administering an effective amount of an antisense molecule which is an oligonucleotide.
9. The method of claim 6, wherein the viral vector further comprises a nucleic acid encoding *MDA-7* in expressible form.
10. The method of claim 1 wherein *RAS* activity is decreased by administering, to the cancer cell population, an effective amount of an agent which inhibits a molecule selected from the group consisting of the epidermal growth factor receptor, *RAF*, MAPK kinase, MAP kinase, and PI3 kinase.

11. A method for inhibiting proliferation and/or inducing cell death of a cancer cell by (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity in the cancer cell.

12. The method of claim 11 wherein the amount of *MDA-7* is increased by introducing, into the cancer cell, a nucleic acid encoding *MDA-7* protein in expressible form.

13. The method of claim 12 wherein the nucleic acid encoding *MDA-7* protein is comprised in a viral vector.

14. The method of claim 13 wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

15. The method of claim 11 wherein *RAS* activity is decreased by administering, to the cancer cell, an effective amount of an anti-*RAS* agent, which may be, for example, an antisense molecule, a ribozyme, a precursor of a triple helix, or a farnesyl transferase inhibitor.

16. The method of claim 15, wherein *RAS* activity is decreased by administering an effective amount of a viral vector encoding an antisense molecule.

17. The method of claim 16, wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

18. The method of claim 15, wherein *RAS* activity is decreased by administering an effective amount of an antisense molecule which is an oligonucleotide.

19. The method of claim 16, wherein the viral vector further comprises a nucleic acid encoding *MDA-7* in expressible form.

20. The method of claim 11 wherein *RAS* activity is decreased by administering, to the cancer cell, an effective amount of an agent which inhibits a molecule selected from the group consisting of the epidermal growth factor receptor, *RAF*, MAPK kinase, and PI3 kinase.

21. A method for inhibiting proliferation and inducing cell death in a population of pancreatic cancer cells having a mutated *K-ras* gene by (i) increasing the

amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity within the population.

22. The method of claim 21 wherein the amount of *MDA-7* is increased by introducing, into one or more cell of the population, a nucleic acid encoding *MDA-7* protein in expressible form.

23. The method of claim 22 wherein the nucleic acid encoding *MDA-7* protein is comprised in a viral vector.

24. The method of claim 23 wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

25. The method of claim 21 wherein *RAS* activity is decreased by administering, to the pancreatic cancer cell population, an effective amount of an anti-*RAS* agent, which may be, for example, an antisense molecule, a ribozyme, a precursor of a triple helix, or a farnesyl transferase inhibitor.

26. The method of claim 25, wherein *RAS* activity is decreased by administering an effective amount of a viral vector encoding an antisense molecule.

27. The method of claim 26, wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

28. The method of claim 25, wherein *RAS* activity is decreased by administering an effective amount of an antisense molecule which is an oligonucleotide.

29. The method of claim 26, wherein the viral vector further comprises a nucleic acid encoding *MDA-7* in expressible form.

30. The method of claim 21 wherein *RAS* activity is decreased by administering, to the pancreatic cancer cell population, an effective amount of an agent which inhibits a molecule selected from the group consisting of the epidermal growth factor receptor, *RAF*, MAPK kinase, MAP kinase and PI3 kinase.

31. A method for inhibiting proliferation and/or inducing cell death of a pancreatic cancer cell having a mutated *K-ras* gene by (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity in the pancreatic cancer cell.

32. The method of claim 31 wherein the amount of *MDA-7* is increased by introducing, into the pancreatic cancer cell, a nucleic acid encoding *MDA-7* protein in expressible form.

33. The method of claim 32 wherein the nucleic acid encoding *MDA-7* protein is comprised in a viral vector.

34. The method of claim 33 wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

35. The method of claim 31 wherein *RAS* activity is decreased by administering, to the cancer cell, an effective amount of an anti-*RAS* agent, which may be, for example, an antisense molecule, a ribozyme, a precursor of a triple helix, or a farnesyl transferase inhibitor.

36. The method of claim 35, wherein *RAS* activity is decreased by administering an effective amount of a viral vector encoding an antisense molecule.

37. The method of claim 36, wherein the viral vector is selected from the group consisting of an adenovirus vector, an adeno-associated virus vector, a retrovirus vector, and a vaccinia virus vector.

38. The method of claim 35, wherein *RAS* activity is decreased by administering an effective amount of an antisense molecule which is an oligonucleotide.

39. The method of claim 36, wherein the viral vector further comprises a nucleic acid encoding *MDA-7* in expressible form.

40. The method of claim 31 wherein *RAS* activity is decreased by administering, to the pancreatic cancer cell, an effective amount of an agent which inhibits a molecule selected from the group consisting of the epidermal growth factor receptor, *RAF*, MAPK kinase, MAP kinase and PI3 kinase.

41. A method for treating a subject having pancreatic cancer, comprising, administering, to the subject, amounts of agents which are effective, in combination, in (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity in cells of the pancreatic cancer.

42. A method for treating a subject having pancreatic cancer, comprising, administering, to the subject, (a) a viral vector comprising an *mda-7* gene in expressible

form; and (b) an antisense *ras* oligonucleotide, in amounts which are effective, in combination, in (i) increasing the amount of the differentiation associated protein, *MDA-7* and (ii) decreasing *RAS* activity in cells of the pancreatic cancer.

43. A method for identifying a suitable cancer cell for treatment with *mda-7*/anti-*RAS* combination therapy, comprising (i) administering, to a test cancer cell, a first agent which increases the amount of *MDA-7* protein in combination with a second agent that decreases *RAS* activity in the cancer cell; (ii) determining whether the cancer cell exhibits at least one characteristic of apoptosis; wherein the presence of a characteristic of apoptosis has a positive correlation with the suitability of the cancer cell for treatment with *mda-7*/anti-*RAS* combination therapy.

44. A method for identifying a suitable cancer cell for treatment with *mda-7*/anti-*RAS* combination therapy, comprising (i) administering, to a culture of test cancer cells, a first agent which increases the amount of *MDA-7* protein in combination with a second agent that decreases *RAS* activity; (ii) measuring the proliferation of cancer cells in the culture; and (iii) comparing the proliferation of cells measured in step (ii) with the proliferation of control cultures of the cancer cells in the presence of the same concentration of first agent or second agent, used alone; wherein if the combination of first and second agent results in a decrease in cell proliferation which is greater than the additive effect of the first agent and the second agent used alone, the cancer cell is suitable for treatment with *mda-7*/anti-*RAS* combination therapy.

45. A viral vector comprising a nucleic acid encoding *MDA-7* protein and a nucleic acid encoding an antisense *ras* nucleic acid, each operatively linked to a promoter element.

46. A method of inhibiting the proliferation of a cancer cell, comprising exposing the cancer cell to an effective concentration of extracellular *MDA-7* protein.

47. The method of claim 46, wherein the extracellular *MDA-7* protein is provided by introducing an isolated *MDA-7* protein into a fluid which contacts the cancer cell.

48. The method of claim 46, wherein the extracellular *MDA-7* protein is produced by secretion from a cell into which an *mda-7* gene, in expressible form, has been introduced.



1. The first step is to identify the problem. This involves understanding the current situation and the goals that need to be achieved.